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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,599	05/31/2005	Joseph M. Penninger	SONN:064US/10416096	8087

32425 7590 05/06/2008

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ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
05/06/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,599	PENNINGER ET AL.	
	Examiner	Art Unit	
	Tekchand Saidha	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *67,68,73,100-102 and 104-130* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *67,68,73,100-102 and 104-130* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Declaration of Dr. M Shuster under 37 CFR 1.132, dated November 1, 2007, recorded at the PTO on 2/21/2008, is acknowledged. The declaration has been considered but not found to be persuasive.

2. In response to the Final rejection (mailed on June 1, 2007), Applicants filed a request for continued examination (RCE) and an amendment received on November 1, 2007. Claims 67-68, 73, 100-102, 104-130 are pending in the instant application and will be examined herein.

Status of claim 103 (cancelled). Claim 103 is not included in the new claim listing. The correct status of all claims must be included in the next response.

3. Any objection or rejection of record which is not expressly repeated in this Office Action has been overcome by Applicant's response and withdrawn.

4. Applicant's arguments filed 11.01.2007 have been fully considered but they are not deemed to be persuasive as explained below.

5. Maintained-New Claim Rejections-Necessitated by amendments - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 67-68, 73, 100-102 & 104-130 remain rejected under 35 U.S.C. 112, first paragraph, and newly added claims 104-106 and 107 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by

weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Claim 67 is drawn to a method of treating an ACE2 decreased state comprising administering to a mammal having hypertension, congestive heart failure, chronic heart failure, acute heart failure, myocardial infarction, arteriosclerosis, renal failure, and/or lung disease a therapeutically effective amount of an ACE2 polypeptide. Claim 68 limits the mammal of claim 67 to include human. Claim 73 limits the method to include co administration of ACE2 polypeptide and ACE inhibitor. Subsequent claims limit the method to include mammal that has lung disease subsequently limiting to respiratory lung and lung cancer respectively. It is also noted that claims 104 & 108-115 further limits the lung disease to include genus of other lung condition including chronic obstructive pulmonary disease, pneumonia, asthma, chromic bronchitis, pulmonary emphysema, cystic fibrosis, interstitial lung disease, primary pulmonary hypertension, pulmonary embolism, pulmonary sacrodosis, tuberculosis, or lung edema. Claims 105-107 limit the method of claim 67 to include ACE2 polypeptide is mouse, rat or human ACE2 polypeptide. Claims 116-124 limits the method genus claims to treating cardiovascular disease such as chronic heart failure and myocardial infarction,

hypertension, etc. Claims 125-130 limits the method genus claims to kidney disease such as kidney failure.

The aspects considered broad are: the breadth of subject population, any method of administration to affect genus of disease associated with ACE2 decreased state by ACE2 polypeptide.

It is noted that as recited, claimed invention reads on a broad genera of protein therapy. Specific considerations for *in vivo* protein therapy includes effective protein production at the target site have to be addressed for an *in vivo* method of treating ACE2 decreased state in a mammal. Although Applicant's specification teaches role of ACE2 is a critical negative regulator of heart contractility and heart function in a ACE2 knockout mouse model, however, the specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to (i) how an artisan of skill would have practiced the claimed method in any mammal, (ii) the claimed method would have resulted in providing the ACE2 in deficient cells in amount sufficient to treat genus of diseases associated with ACE2 decreased state by administering ACE2 polypeptide to any site. As will be shown below, these broad aspects as well as limitations were not enabled for the claimed invention at the time of filing of this application because neither the specification nor the art of record taught sufficient guidance to practice the claimed invention. For purposes to be shown in the state of the prior art, the question of lack of enablement is discussed.

The invention describes compositions and methods for use in diagnosing and treating heart, lung and kidney diseases, including hypertension, coronary heart disease, heart and kidney failure, lung edema, and lung injury such as in toxic shock or artificial ventilation (pp 1). The specification contemplates new paradigm for the regulation of the renin -angiotensin system and shows a completely new and unexpected usage of ACE2 (page 2). Pages 2-7 broadly summarize the invention and provide a brief description of figures. Pages 7-31 provide a detailed description of preferred embodiments, therapeutic methods, screening of ACE2 activator, knockout

mammals kits, definition of terms, and other therapeutic aspects of ACE2 and characterization of ACE2 as a negative regulator of RAS and its role in blood pressure control. Pages 31-44 describe specific example showing studies in ACE2 knockout mice and mapping of ACE2 to QTL on the X-chromosome in hypertensive rat strains. It is noted that instant specification describes ACE2 mapping to a QTL on the X-Chromosome in three hypertensive rat strains, it is noted that ACE2 in mouse and rat is predominantly expressed in kidney and heart, with little expression in lung and liver (see Figure 1c and example). The specification also exemplified that ACE2 protein expression was markedly reduced in SBH/y animals that are fed a normal diet, while an increase in blood pressure of SBH/y rats following a 4-week diet of DOCA-salt correlated with further decreased ACE2 protein expression (see Figure 2B). It is emphasized that specification describes that in order to test whether ACE2 has any essential role in the cardiovascular physiology and the pathogenesis cardiovascular diseases, the mouse ACE2 gene was cloned and an ACE2 knockout mouse was made (see example and Figure 3a-c). It is noted that loss of ACE2 had no apparent direct effect on blood pressure homeostasis in this defined mouse background however backcross with mutant mice to other mouse backgrounds show the role of ACE2 in blood pressure control similar to human (see example and Figure 4). The western blot of kidney of these ace2 deficient mice show enhanced expression of hypoxia inducible factor-1alpha (HIF1-.alpha.) and vascular endothelial growth factor (VEGF). The examples further describe specific phenotype of this knockout mice showing slight wall thinning of the left ventricle and increased chamber dimensions (see Figure 5) and anterior left ventricular wall (AW) and increase in the left ventricle end diastolic dimension. It further characterizes that ACE2 functions as a negative regulator of the RAS and controlling endogenous levels of AngII. Using double knock out specification shows that ablation of ACE expression on an ace2 mutant background completely abolished the heart failure phenotype of ace2 single knockout mice (see figure 8a-c). Specification describes that ACE2 knockout mice showed a significantly more severe response in lung elastance than wild type mice. Thus, specification contemplates the significance of ACE2 in protecting lungs from acute acid-induced injury (see example,

pages 40-43). However, such broad disclosure does not demonstrate the information required by the Artisan to reasonably predict that any protein could be delivered in any cell of any mammal at therapeutic effective levels. The art of protein therapy and their delivery at the time of the filing of this application was unpredictable wherein protein is expressed in an individual suffering from cardiovascular or lung disorder.

The specification does not disclose the effectiveness of the method of the instant invention in treating any ACE2 decreases state. Nor does it teach the effectiveness of the method in increasing the level of ACE2 in any cell and reversal of any pathology or condition associated with decreased ACE2 state. The specification only teaches role of ACE2, but fails to disclose any method in treating any condition by administering any composition of ACE2. The specification teaches only the role of ACE2 in the heart failure, hypertension and lung pathology, but fails to disclose the efficacy of using said any method wherein administering a ACE2 composition resulted in the treatment of any disorder. The examples in the specification do not disclose a **therapeutic** effect in any patient after therapy with any composition and/or treating with any composition. Although working examples are not required, particularly in predictable art, the presence or absence of working example is one of the factors that must be considered, particularly in the unpredictable arts. In the absence of specific guidance, one of ordinary skill in the art would be required to engage in undue experimentation to make and use the invention as claimed.

It is emphasized that the mechanism of development of each disease is different, the parameters of treating any particular disease associated with ACE2 decreased state such as heart failure may be different, from those used in treating another disease such as lung cancer and therefore, the reversal of the symptoms in one case due to any therapy can not be predictive of the effects in another. Such parameters will include the site of action of the protein, cell types and tissues affected by the ACE2 deficiency. In the instant case, specification has exemplified most of its finding in a ACE2 knockout mice. The specification teaches the different phenotype of ACE2 knockout mice and ACE/ACE2 double knockout mice. Holschneider et al. (Int J Devl Neuroscience, 2000,

18: 615-618) state that single genes are often essential in a number of different physiological processes. Hence deletion of an individual gene in the instant case ACE2 may prove so drastic or so widespread as to create an amalgam of phenotypes whose interpretation becomes confounded by the interaction of various new physiologic changes (pp 615). Holschneider et al discuss various factors that contribute to the resulting phenotype of transgenic mice, including compensatory system that may be activated to mask the resulting phenotype; these compensatory changes may be due to differential expression of another gene, which may be regulated by the downstream product of the deleted gene. Thus, the specification at best provide some evidence of role of ACE2 deficiency in hypertension and lung disorders using a transgenic knock out mice, but these findings could not be predictive of any method of treating any condition by delivering a nucleic acid or ACE2 protein. It is noted that claims as recited and the specification is silent about whether a nucleic acid encoding ACE2 protein or ACE2 polypeptide would be in active form when administered via any route at any site as broadly recited in rejected claims. Therefore, these molecules may not even act as an activator. It is also noted decreased ACE2 decreased state include plurality of cardiac disorder including atherosclerosis. Prior to instant invention, Tailleux et al (2003) describe that lipid and lipoprotein metabolism is dissimilar between mice and humans. In addition, the regulations of genes encoding proteins that are involved in lipid and lipoprotein metabolism are not identical between humans and mice and thus data obtained in the mouse are not always directly relevant to humans. Third, the mouse is highly resistant to atherosclerosis and does not develop atherosclerotic lesions spontaneously. Tailleux et al further teach, "homologous recombination technology allows the extinction of a specific gene (knockout). However, in such mouse models, the functionality of all metabolic pathways is not necessarily maintained, and thus the model only provides information about whether a ligand requires the presence of the deleted gene. However, in most murine models created by genetic modification, lipoprotein levels are insufficiently altered to induce the development of atherosclerotic lesions. Thus, in absence of any direct evidence in the specification or prior art it would be difficult to predict the role of administering ACE2 activator. Thus, at the time of filing, the

resulting phenotype of a knockout was considered unpredictable. Furthermore, contrary to applicants findings, prior art teaches a method of treating an ACE-2 associated state in humans suffering from a blood pressure related disorder, such as congestive heart failure by administering a therapeutically effective amount of an ACE-2 inhibiting compound, such that the ACE-2 associated state is treated (Acton et al US Patent no 6,632,830). Furthermore, Acton et al contemplate administering an effective amount of an ACE-2 inhibiting compound and an effective amount of an ACE inhibitor to treat cardiac conditions which is contrary to the teaching of instant application that intend to treat same conditions by administering ACE2 activator (see column 3, lines 54-67 bridging to column 4). Therefore, the observations of Acton et al in the prior art and the stand taken that phenotypes disclosed in the instant application cannot be solely due to loss of ACE2 gene. It is apparent that in absence of any specific showing that administering Ace2 polypeptide would results in result in any therapeutic effect, an artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because of the art of treating cardiac or lungs condition by administering ACE2 activator showed conflicting results and was not completely resolved at the time of filing of this application.

The specification also contemplates delivering polypeptides to any cells using *in vivo* delivery vehicles such as but not exclusive to liposomes. In summary, specification does not specifically provide any specifics in term of what and where the therapeutic composition would be administered for an optimal therapeutic response, it is noted that, there are art-recognized limitations of using liposome and there is no teaching or contemplation as to how an artisan of skill would have addressed these limitations. For example, Filion et al (Br J Pharmacol. 1997;122(3): 551-557) listed several adverse effects associated with cationic lipids or cationic liposome (table 2, pp 18) such as immunomodulation of animals, complement activation, induction of pulmonary inflammation and toxicity. The specification does not provide any guidance as to what doses of the cationic lipid would be used in the method without eliciting adverse effects. It is noted that the prior art at the time of filing of this application did not provide any guidance in this regard either. Davis et al (Current Opinion in Biotechnology 2002,

13:128–131) evinces an optimistic outlook for non-viral delivery system but states "perfect system does not currently exist". Davis et al describe problems associated with non-viral delivery system, which includes obstacles in manufacturing, toxicity, formulation and stability.

With regards to evaluation of efficacy of a therapeutic protein, dosing, clearance and efficacy of the product, preclinical evaluation for toxicity and immunogenicity are important steps. It is noted that toxicity with proteins often presents differently that with small-molecule pharmaceutical drugs (Scientific Considerations Related to Developing Follow-On Protein Products, 2004, p. 3, paragraph 1). Further, immunogenic responses in patients can be triggered by large-molecules products, product-related or process-related impurities raising unwanted antibodies. Additionally, the way in which unwanted immunogenicity may present in different patients is unpredictable and varied, even with identical amino acid sequences; immunogenicity to the product can vary dramatically (Scientific Considerations Related to Developing Follow-On Protein Products, 2004, p. 4-5). Thus, preclinical evaluation for efficacy and immunogenicity of a therapeutic protein is vital for the development of therapeutic protein. It is noted that, it is important to assess the half-life and clearance of the protein as the terminal elimination half-life of related products can vary drastically. For example, six companies manufacture FDA-approved versions of human growth hormone, with the same number of amino acid and very similar molecular weights, presented terminal half-life from 1.75 to 10 hours. Thus, such large variations can impact the effectiveness of the product and the as the body's immune response to it (Scientific Considerations Related to Developing Follow-On Protein Products, 2004, p. 5, paragraph 1). Hence, the risk of immunogenicity should be assessed for each product and characterized with appropriate therapeutic response. In the instant case, specification provides no guidance of administering any polypeptide for the treatment of any condition associate with ACE decreased state. A reasonable correlation must exist between the scope of the claims and scope of enablement set forth in the specification as filed. Without sufficient guidance, the mere enumeration of treatment of genus of diseases associated with decreased ACE2 state in any mammal is unpredictable and the

experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. With regards to evaluation of a therapeutic protein, dosing, clearance and efficacy of the product, Prior art teaches that preclinical evaluation for immunogenicity are important steps. The specification contemplates administration of **soluble rhACE2** from a specific source, in a manner that increases the level of ACE2 by direct administration; however, the specification fails to teach any immunogenicity or efficacy of any such composition in any mammal because of said administration. Hence, one skill in the Art at the time of the invention could not reasonably predict that the use of Ace2 protein therapy will treat any condition associated with ACE2 decreased state in any mammal.

In conclusion, in view of breadth of the claims and absence of a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for the claimed inventions. The specification and prior art do not teach a method of *in vivo* delivery of any ACE2 activator such that it transduces cells sufficiently to elicit a pharmacological response for a desired duration in any tissue of any mammal suffering from any condition associated with decreased ACE2 state. An artisan of skill would have required undue experimentation to practice the method as claimed because the art of gene and protein therapy and *in vivo* delivery and treatment of any condition associated with ACE2 decreased state in general by gene and protein delivery *in vivo* was unpredictable at the time of filing of this application as supported by the observations in the art record.

Response to Arguments

Applicant arguments and amendments to claims filed on 03/20/2007 have been fully considered but they are not fully persuasive. Applicant asserts that he rat and mouse studies in the present specification demonstrate that an ACE2 decreased state is associated with cardiovascular, renal, and lung diseases. For example, decreased ACE2 mRNA and protein levels were observed in the kidneys of hypertensive rats. Applicants also argue ACE2 knockout mouse shows detrimental effects in the kidneys,

heart defects, and increases the susceptibility of the lungs to injury. Based on these studies applicants assert that those of ordinary skilled in the art would have appreciated the therapeutic benefit of a method of treating an ACE2 decreased state comprising administering to a mammal having genus of heart, renal and/or lung disease by administering an effective amount of an ACE2 polypeptide (see page 7). Applicants also cite the declaration by Dr. Neu in support of enablement (see pages 4-5, section 7-9).

In response, it is noted that breadth of independent claim 67 recite a method of treating any mammal including humans having genus of heart, renal or lung conditions by administering an effective amount of ACE2 polypeptide. Examiner would agree that prior art taught physiological role of ACE in variety of different condition including those specifically recited here. However, Examiner had also cited prior art references that taught method of treating an ACE-2 associated state in humans suffering from a blood pressure related disorder, such as congestive heart failure by administering a therapeutically effective amount of an ACE-2 inhibiting compound, (Acton et al US Patent no 6,632,830, art of record). It was indicated that Acton et al contemplated administering an effective amount of an ACE-2 inhibiting compound including ACE2 polypeptide and an effective amount of an ACE inhibitor to treat cardiac conditions which is contrary to the teaching of instant application that intend to treat same conditions by administering ACE2 agonist (see column 3, lines 54-67 bridging to column 4). Given this lack of reasonable predictability in the prior art, the Artisan would require a large amount of information from Applicant's examples specially in terms of reliability of animal model that could be extrapolated to genus of different cardiac, renal and lung pathologies that would with provide reasonable predictability in the treatment of these disorders in humans.

With respect to applicants argument that specification teaches decreased ACE2 mRNA and protein levels were observed in the kidneys of hypertensive rats and declaration by Dr. Neu citing Danilczyk et al. (2004 and 2006) (Exhibits 2 and 3, respectively, art of record) to indicate the role of loss of ACE2, it is emphasized that the issue is not whether ACE2 has potential role in heart, lung or renal condition. The issue is whether specification provided adequate guidance at the time of filing of this

application to an artisan to make and use the invention. Examiner had cited references to indicate that at the time of filing, the resulting phenotype of a knockout animal was considered unpredictable. For instance, Holschneider et al. (Int J Devl Neuroscience, 2000, 18: 615-618) state that single genes are often essential in a number of different physiological processes. Thus, deletion of an individual gene in the instant case ACE2 may prove so drastic or so widespread as to create an amalgam of phenotypes whose interpretation becomes confounded by the interaction of various new physiologic changes (pp 615). Holschneider et al discuss various factors that contribute to the resulting phenotype of transgenic mice, including compensatory system that may be activated to mask the resulting phenotype; these compensatory changes may be due to differential expression of another gene, which may be regulated by the downstream product of the deleted gene. These arguments are further supported by applicants own post filing art cited by the applicants wherein Danilczyk et al. (2004 Exhibit 2) describe the varying effects seen by different independent groups (page 2717, Col.1, para.1). Further, Danilczyk et al. (2004, exhibit 1) state, "Taken together, it still remains unclear what the net effect is of the interplay between angiotensin II and the ACE2-mediated peptides angiotensin 1-7 and angiotensin 1-9. It has to be clarified whether, in the relative absence of ACE2, an angiotensin II effect predominates, leading to vasoconstriction and hypertension, or whether compensating mechanisms maintain normal or lower blood pressure dependent on defined genetic backgrounds. The mechanism that regulates blood pressure through the production of angiotensin II was thought to be well understood, but given the complexity of the systems involved, additional studies on mutant mice and specific blocking agents are needed to further our understanding of the physiologic role of ACE2 in blood pressure regulation". Similarly Danilczyk et al. (2005 Exhibit 3) cited by applicant describe ACE2 expression increases in the infract followed by increased ACE2 expression in the myocardium surrounding the ischemic zone after coronary artery ligation in rats. .."ACE2 expression has affected the severity or outcome of myocardial infarction remains contentious. However, what has emerged from recent studies appears to be the involvement of ACE2 in increasing the content of cardiac Ang I-7". In addition, Examiner had indicated that prior art

summarized by the reference of Tailleux et al (2003) describe that lipid and lipoprotein metabolism is dissimilar between mice and humans. The regulations of genes encoding proteins that are involved in lipid and lipoprotein metabolism are not identical between humans and mice and thus data obtained in the mouse are not always directly relevant to humans (supra). In view of preceding discussion, it is apparent that disclosed animal models were not predictive of animal model for treating genus of cardiac or lung conditions embraced by the breadth of the claims. The cited art including those cited by applicants clearly show that exact role of ACE2 in the disease condition was evolving at the time of filing of this application which is evident by applicant's own post filing art. It is noted that results in the specification as well as prior art only indicated the potential role of ACE2 in increasing the content of cardiac Ang I-7 in small animal model that was not predictive of treating different conditions in humans. The declaration by Dr. Neu fails to establish the nexus between the phenotype seen in the mouse model to plurality of disease embraced by the claims. In addition, it is further unclear whether instant method using the mouse model would be predictive of method of treating plurality of conditions by delivering ACE2 protein. An artisan have to carry out extensive experimentation to first establish the reliability of animal model and then make and use the invention, and such experimentation would have been undue because of the art of treating cardiac or lungs condition by administering ACE2 activator showed conflicting results and was evolving at the time of filing of this application.

Applicants also cite the reference by Imai et al. (Nature, 436:112-116 (2005); IDS reference C61)) to further support that those of skill in the art can make and use the claimed invention without undue experimentation (see Neu Declaration, para. 7). Applicants also cite studies in piglet to show the role of acute lung injury (see page 8 and 9 of the argument).

In response to applicant's argument it is noted that claims are directed to a method of treating an ACE2 decreased state by administering an ACE2 polypeptide to a mammal having any cardiac, renal and or lung disease. The unpredictability of animal model disclosed in the specification for disease conditions and lack of nexus between phenotype seen in knock out mouse to humans have been discussed in preceding

section. The specification defines "lung disease' as chronic obstructive pulmonary disease, pneumonia, asthma, chromic bronchitis, pulmonary emphysema, cystic fibrosis, interstitial lung disease, primary pulmonary hypertension, pulmonary embolism, pulmonary sarcodosis, tuberculosis and lung cancers (See para. 31), while adult respiratory distress syndrome (ARDS) is a serious form of acute lung injury. It is noted that specification further describes that trauma, severe sepsis (systemic infection), diffuse pneumonia and shock are the most serious causes of ARDS, and among them acid-induced lung injury is one of the most common cause (see para. 149 of the published application).

In the instant case, the methods described in post filing art at best provide support for role of ACE polypeptide in treating acute acid-induced injury in mouse. However, instant method claims 67-68, 73, 100, 102, 14-107 read on treating any mammal including humans having any lung injury. It is noted that specification describes that adult respiratory distress syndrome (ARDS) is a serious form of acute lung injury. In the instant case, Imani et al disclose injection of rhuACE2 into acid-treated Ace2 knockout mice decreased the degree of acute lung injury, as assessed by lung elastance (Fig. 2d) and pulmonary oedema formation (Fig. 2e), while injection of rhuACE2 protein into acid-treated wild-type mice, lung function (Fig. 2f). However, neither the declaration by Dr. Neu nor the disclosure of Imani show the effect of acid induced lung injury resulting systemic infection, diffuse pneumonia, shock or any other chronic injury condition embraced by the breadth of the claims which are the most serious form of acute lung injury. It is noted that the features upon which applicant relies (i.e., acute lung injury) are not recited in the rejected claims. It is noted that ARDS could be caused by many different reasons and neither specification nor post filing art sufficiently shows that severe sepsis (systemic infection), diffuse pneumonia and shock resulted in the mouse disclosed by Neu et al. In addition, the animal model disclosed by Lockinger is different then one disclosed in the instant specification, and therefore cited report cannot be used for the enabling support of the instant claims as cited arts uses method that is different from the instant disclosure. It is apparent that in spite of disclosure providing guidance in terms of reducing acute lung injury after administering

ACE2 polypeptide, it does not provide any guidance in terms of its functional involvement in genus of lung disease characterized by chronic lung conditions that could be extrapolated in treating conditions in any mammal including humans. Further, the art of record fail to establish this relationship and the specification lacks any teaching that establishes the function of ACE2 in genus of different chronic lung condition including lung cancer.

Applicants provide Dr. Neu's declaration to overcome unpredictabilities of administering ACE2 polypeptide for treating genus of cardiac, renal and or lung injury via any route of administration. The declaration by Dr Neu is persuasive in part; hence, rejections pertaining to route of administration and ACE2 polypeptides are withdrawn.

With respect to applicants argument that testing for the full safety and effectiveness of a particular drug for human use is more properly left to the Food and Drug Administration (FDA). Applicants also argue that the use of protein therapy in the treatment of diseases is well-known in the medical field (also see Neu Declaration, para. 6). Applicants cite use of Epogen®, which is a protein therapy.

In response, it is it is emphasized that Examiner had no intention to raise any toxicity or safety issue arising from administering ACE2 polypeptide. The discussion is merely intended to address problems that are associated with administering polypeptide Furthermore, Examiner cited the reference to indicate that human growth hormone, with the same number of amino acid and very similar molecular weights, presented terminal half-life from 1.75 to 10 hours. Thus, such large variations can impact the effectiveness of the product and the as the body's immune response to it. Furthermore, unwanted immunogenicity may present in different mammal is unpredictable and varied, even with identical amino acid sequences; immunogenicity to the product can vary dramatically. The guidance provided by the specification amounts to invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses a subset of phenotypes that fall within the broad scope of genus of lung injury. The specification fails to teach any immunogenicity or efficacy of any such composition in any mammal because of said

administration would results in any therapeutic effect particularly since none of claim recite any method step to indicate that ACE2 protein expression was ever achieved by administration ACE2 polypeptide in the mammal for the treatment plurality of conditions. In absence of any such method step it is reasonable to state that one skill in the Art at the time of the invention could not reasonably predict that the use of Ace2 protein therapy will treat any condition associated with ACE2 decreased state in any mammal as embraced by the breadth of the claim.

New Arguments:

Rejection by Examiner Singh is reproduced here. The difference in Applicants' and Examiner's arguments appears to be the 'therapeutic component' and the specificity of the method. A **therapeutically** effective amount of soluble rhACE2 from a specific source (not ACE2 from any source) that has been used for treatment – amounts to a 'cure', and the invention is not enabled for such a claim. No treatment method of any of the diseases (including cancer) is supported by the instant specification to have resulted in a cure.

6. ***Claim Rejections - 35 USC § 112*** (second paragraph)

Claims **67-68, 73, 100-102, 104-107** are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 67 recites the phrase 'ACE-2 decreased state'. The phrase is not clear in its meaning and the specification or the art does not clarify the meaning. Further, it is not clear how the 'ACE-2 decreased state' is measured.

Claims **68, 73, 100-102, 104-107** are included in the rejection for failing to correct the defect present in the base claim(s).

7. Claims **67-68, 73, 100-102, 104-130** rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: For claims 67-68, 73, 100-102, 104-1130 a step to determine the 'decreased state of ACE-2' will be

important to know how much of the ACE-2 is required. It would be important to determine what level of ACE-2 is considered 'ACE-2 decreased state' and with reference to which disease.

8. ***Conclusion***

No Claim is allowed.

9.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha whose telephone number is (571) 272 0940. The examiner can normally be reached on 8.30 am - 5.00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272 0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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April 28, 2008